a) hybridizing a first oligonucleotide to the target nucleic acid and hybridizing a second oligonucleotide to an adjacent region of the target nucleic acid;

b) contacting the hybridized first and second oligonucleotides with a cleavage enzyme to form a cleavage product; and

c) detecting the cleavage product by mass spectrometry as an indication of the presence of the target nucleic acid.

REMARKS

A check for the fees for a three-month extension of time and a Petition under 37 C.F.R. §1.48(b) accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 50-1213.

In a Preliminary Amendment dated April 5, 2001, the paragraph on page 108, lines 15-21, was amended and included a formula. The basis for the amendment can be found at page 108, lines 15-21, of the specification. The amendment seeks to further amend this paragraph by correcting an obvious typographical error in the equation. Thus, no new matter has been added.

Claims 4-17, 30-34, 43-54, 60-64, 71-81, 83-85 and 98-108 are pending in this application. Claims 30, 51, and 52 are canceled without prejudice or disclaimer. Claims 60-64, 71-81, and 83-85, which are withdrawn from consideration as being drawn to non-elected subject matter, are cancelled herein without prejudice or disclaimer. Applicant expressly reserves the right to file a divisional application(s) to the subject matter of claims 60-64, 71-81, and 83-85.

New claims 101-108 reinstate original claims 35-42 which were inadvertently cancelled in an Election and Preliminary Amendment mailed March 18, 2002. Claims 35-42, and thus claims 101-108, are the subject of a Petition from a Requirement for Restriction and a Requirement for Election of Species under 37 C.F.R. §1.144, filed by applicant on July 10, 2002.

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Claims 32-34 and 100, which are withdrawn from consideration because they are drawn to non-elected subject matter, are the subject of a Petition from a Requirement for Restriction and a Requirement for Election of Species under 37 C.F.R. §1.144, filed by applicant on July 10, 2002. The arguments made therein are repeated below.

Claim 4 is amended to more distinctly claim the subject matter claimed by the applicant. Basis for the amendment can be found throughout the specification and the original claims as filed. For example, support for the amendment to include the recitation —storing the database on a computer-readable medium— can be found on page 19, lines 24-26; page 20, lines 11-13; page 22, lines 20-25; and claim 43 as filed.

Claim 5 is amended to more distinctly claim the subject matter claimed by the applicant. Basis for the inclusion of the recitation —other biological sample— in claim 5 can be found throughout the specification (see page 6, lines 21-25, page 7, lines 12-16, and original claims 8, 32, 25, and 88). Claim 8 is amended to more distinctly claim the subject matter, basis for which can be found throughout the specification (for example, see page 19, lines 24-26; page 23, lines 24-26; and page 25, lines 9-15). Claims 9 and 100 are amended to correct minor informalities and to correct an obvious typographical error. Claims 53 and 54 are amended to correct dependency.

Claim 43 is amended to more distinctly claim the subject matter claimed by the applicant. Basis for the inclusion of the recitation —wherein the database is a relational database— can be found throughout the specification (see page 4, lines 14-15 and page 19, lines 19-24).

Therefore, no new matter is added nor are any amendments made to change the scope of the claims nor to avoid art of record. The amendments should place the claims and the application into condition for allowance.

Included as an attachment is a marked-up version of the specification paragraphs and claims that are being amended, as per 37 CFR §1.121.

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PETITION FROM RESTRICTION REQUIREMENT AND ELECTION OF SPECIES

Applicant petitioned for reconsideration and removal of the Restriction Requirement as between Groups II and V, and as between Groups II and XVI, on July 10, 2002. The Office Action, mailed September 21, 2001, urges that the Restriction Requirement is based on the allegation that the various Groups are patentably distinct. Applicant respectfully submits that Group II is related to each of Groups V and XVI as subcombination/combination for which a showing of two-way distinctness is required. Such showing has not been made.

Restriction Between Groups II and V

Group II, claims 4-17, 30-31, 43-54, and 98-99, includes claims directed to a database containing data representative of a plurality of healthy organisms, and is restricted further to an election of species to one of the parameters contained in claim 9. Group V, which includes claims 32-42 (now claims 32-34 and 101-108), includes claims directed to a system for high throughput processing of biological samples that includes an automated process line, a data analysis system, a control system, and a database of claim 8. Hence, Group II is related to Group V as a combination/subcombination, where the system is the combination and the database is the subcombination. For groups related as a combination/ subcombination, a showing of two-way distinctness is required.

Inventions that are related as a combination and subcombination are distinct and restriction may be proper **only if** it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability **and** that the subcombination has utility by itself or in other combinations (MPEP 806.05(c), paragraphs 1 and 3). Group II includes claims directed to a database. For example claim 8 of Group II is directed to:

8. (Amended) A database, comprising:
datapoints representative of a plurality of healthy organisms from whom biological samples are obtained; and
an indexer that identifies each organism, wherein
a) each datapoint is associated with data representative of the organism type and other identifying information by the indexer;

b) the database is stored on a computer-readable medium; and
c) the database is sortable.

Group V includes claims directed to a system for high throughput processing. For example, claim 32 of Group V is directed to:

> 32. A system for high throughput processing of biological samples, comprising:
> a process line comprising a plurality of processing stations, each of which performs a procedure on a biological sample contained in a reaction vessel;
> a robotic system that transports the reaction vessel from processing station to processing station;
> a data analysis system that receives test results of the process line and automatically processes the test results to make a determination regarding the biological sample in the reaction vessel;
> a control system that determines when the test at each processing station is complete and, in response, moves the reaction vessel to the next test station, and continuously processes reaction vessels one after another until the control system receives a stop instruction; and
> **a database of claim 8**, wherein the samples tested by the automated process line comprise samples from subjects in the database.

In this instance, the combination, the system of claim 32, includes the database of Group II and a known automated process line (see page 40 of the instant specification which states: "[t]he computers and databases can be used in conjunction, for example, with the APL system (see copending U.S. application Serial No. 09/285,481), which is an automated system for analyzing biopolymers"). Hence, absent evidence to the contrary, Group V, the combination, requires the particulars of the database of Group II, the subcombination, for patentability. Example II of MPEP 806.05(c) states:

> If there is no evidence that [the] combination...is patentable without the details of [the subcombination], restriction should not be required. Where the relationship between the claims is such that the separately claimed subcombination...constitutes the essential distinguishing feature of the combination...as claimed, the inventions are

not distinct and a requirement for restriction must not be made, even though the subcombination has separate utility.

Therefore, as between Group II and Group V restriction is not proper.

The Examiner found applicant's traversal unpersuasive, stating in the Office Action mailed May 13, 2002 that "the system for high throughput processing of biological samples [of Group V] does not necessarily have to be utilized to analyze the [claimed] biomarkers" and the claimed subject matter "could be practiced without the system of high throughput analysis, for example by traditional serum level analysis."

The Examiner's assertion does not appear to address either prong of the two-way distinctiveness test required for restriction of subject matter related as subcombination/combination. As demonstrated, the subject matter of Groups II and V is related by the database of Group II. Claim 8 of Group II is directed to a database. Claim 32 of Group V is directed to a system that includes the database of claim 8, and one cannot practice the claimed subject matter of claim 32 and its related claims without the database.

It is respectfully submitted that the Examiner has not complied with the requirements for restriction as outlined in MPEP 806.05(c), and has not shown that the combination does not require the subcombination to be patentable. Therefore, applicant contends that restriction is not proper and petitions for removal of the Restriction Requirement as between Groups II and V.

Restriction Between Groups II and XVI

It is respectfully submitted that the Restriction Requirement as between Groups II and XVI is improper because the Groups are not patentably distinct, for essentially the same reasons as discussed above. Group II, the subcombination, includes claims directed to a database containing datapoints representative of a plurality of healthy organisms. Group XVI, the combination, is directed to a system for high throughput processing of biological samples that includes a database of Group II. For example, claim 100, in Group XVI, recites:

> A system for high throughput processing of biological samples, comprising:
>
> a database of claim 8, wherein the samples tested by the automated process line comprise samples from subjects in the database; and
>
> a mass spectrometer for analysis of biopolymers in the samples.

Thus, claim 100 is directed to a combination that includes a database of claim 8, the subcombination. Because Group XVI is directed to the combination of the database of claim 8 and a mass spectrometer, and a mass spectrometer is not a basis for patentability, Group XVI requires the particulars of the database of claim 8 from Group II for patentability. Thus, the combination as claimed requires the subcombination as claimed for patentability. Therefore, as between Group II and Group XVI, restriction is **not** proper.

The Examiner's assertion that the claimed subject matter "could be practiced without the system of high throughput analysis, for example by traditional serum level analysis," is not correct. The assertion does not address the issue of distinctness. Claim 100, which is directed to a combination that includes a database of claim 8 as the subcombination, is specifically directed to a system for high throughput analysis for processing of biological samples that employs a database of Group II.

Obviousness-Type Double Patenting

Applicants respectfully submit that if this division of claims is maintained, applicant ultimately could be granted multiple patents that include claims with overlapping subject matter. For example, claims 8, 32, and 100 (discussed above) could ultimately end up in different patents. If claim 8 issues first, obvious-type double patenting between claims 8 and 32 or between 8 and 100 in a later issuing patent could not be held. MPEP 806, paragraph 3 states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Applicant, thus, ultimately could obtain multiple patents with different expiration dates that include claims with overlapping subject matter. The Office would be precluded from requiring terminal disclaimers. In light of the above arguments, applicant petitioned for removal of the restriction requirement as between Groups II and V and Groups II and XVI.

Requirement for Election of Species

Applicant also petitioned for removal of the Requirement for Election of Species for the elected claims. Elected Group II, which includes claims 4-17, 30-31, 43-54, and 98-99, includes claims directed to a method of producing "healthy patient" databases, which include as datapoints the answers that healthy patients give to various questions. The subjects of the database are "healthy" subjects; it is the selection of such subjects as the source of data for a database that is a subject of the application and claimed subject matter. The Examiner has imposed an election of species, requiring the selection of one of the parameters or datapoints contained in claim 9.

Election of species is a search tool intended to be used where there is a generic claim that encompasses a large number of species, such as a claim that sets forth a formula for an organic compound that includes numerous compounds, each of which has a large number of possible alternatives. In such instance, it is impossible to search all of the combinations and permutations of the compounds encompassed within the scope of the claims, and the applicant is entitled to have a reasonable number of species searched.

In this instance, the subject matter for which a search would be conducted is a database, not the datapoints that constitute the database. The claims are directed to databases and methods of using databases that include sets of parameters associated with healthy subjects in populations. The parameters include ethnicity, age, sex, medical history, and genotypic information, and the database can then be sorted using these parameters.

Applicant respectfully submits that the requirement for election of a single parameter of instant claim 9 as a "species" is inconsistent with the subject matter of the instant claims. A database composed of a single parameter or type of datapoint could not be sorted by parameter if only one parameter is contained therein. Moreover, such requirement could violate applicant's right to have all species that form a single general inventive concept included in a single application (see, MPEP 1893.03(d)).

In view of the above, applicant petitioned for removal of the restriction requirement as between Groups II and V and between Groups II and XVI. It is respectfully submitted that the restriction requirement as between Groups II and V and Groups II and XVI is improper because Group II is related to Group V and to Group XVI as a combination/subcombination for which a showing of two-way distinctness is required. The Groups are not patentably distinct because the combination requires the subcombination as claimed in order to be patentable. Because applicant elected Group II, with traverse, in the instant application, applicant petitioned that Groups II, V and XVI (claims 4-17, 30-54, and 98-100) be combined for examination herein. Further, for the above reasons, applicant petitioned for removal of the Requirement for Election of Species in Group II.

ALLEGED DUPLICATE CLAIMS

The objection raised by the Examiner that claim 43 is a duplicate of claim 4 is obviated by the amendment of claim 43 herein to include the recitation —wherein the database is a relational database—. In light of the amendment, Applicant respectfully requests that the objection be withdrawn.

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THE REJECTION OF CLAIMS 4-17 UNDER 35 U.S.C. §101

Claims 4-17 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter because the Examiner asserts that "the method of producing a database which simply manipulates data by gathering information and entering it is non-statutory." The Examined further contends that the claimed subject matter does not meet the standard of being immediately useful because "the need to do excessive work after generating the library does not meet the 'concrete, tangible, and useful' result standard set forth in MPEP 2106." The rejection is respectfully traversed.

RELEVANT LAW

In **State Street Bank & Trust Co. v.Signature Financial Group, Inc.**, 149 F.3d 1368, 47 USPQ2d 1596 (Fed. Cir. 1998) found that as long as the computer program, method or process, "produces a useful, concrete and tangible result" then the claimed subject matter is patentable:

> Today, we hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"—a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades. The district court erred by applying the Freeman-Walter-Abele test to determine whether the claimed subject matter was an unpatentable abstract idea. The Freeman-Walter-Abele test was designed by the Court of Customs and Patent Appeals, and subsequently adopted by this court, to extract and identify unpatentable mathematical algorithms in the aftermath of Benson and Flook. See In re Freeman, 573 F.2d 1237, 197 USPQ 464 (CCPA 1978) as modified by In re Walter, 618 F.2d 758, 205 USPQ 397 (CCPA 1980). The test has been thus articulated:
>
> First, the claim is analyzed to determine whether a mathematical algorithm is directly or indirectly recited. Next, if a mathematical algorithm is found, the claim as a whole is further analyzed to determine whether the algorithm is "applied in any manner to physical elements or process steps," and, if it is, it "passes muster under § 101." In re Pardo, 684 F.2d 912, 915, 214 USPQ 673, 675-76 (CCPA 1982) (citing In re Abele, 684 F.2d 902, 214 USPQ 682 (CCPA 1982)).

> The question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to —process, machine, manufacture, or composition of matter— but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See In re Warmerdam, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." Alappat, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss. . . .
>
> Similarly, In re Schrader, 22 F.3d 290, 30 USPQ2d 1455 (Fed. Cir. 1994), while making reference to the business method exception, turned on the fact that the claims implicitly recited an abstract idea in the form of a mathematical algorithm and there was no "transformation or conversion of subject matter representative of or constituting physical activity or objects." 22 F.3d at 294, 30 USPQ2d at 1459 (emphasis omitted).

Further, in In re Lowry 32 USPQ2d 1031 (CAFC 1994) the court held that a computer memory containing a particular type of data structure is patentable.

ANALYSIS

The Examiner urges that the claimed subject matter is non-statutory because "although one could argue that the database could be useful in further research to identify potential risk for patients, there is no specificity as to what types of risks are being assessed" and that there is a "need to do extensive work after generating" the database, and thus "the library does not meet the concrete, tangible, and useful result standard set forth in MPEP 2106."

Applicant respectfully disagrees. The application discloses numerous uses for the database claimed, and there is no evidence to support the allegation of the Examiner that there is a need to do extensive work after generating the database in order to make it useful.

The Office has the burden of establishing a *prima facie* case that the claimed subject matter as a whole does not produce a useful result. Only when the claim is devoid of any limitation to a practical application in the technological arts should it be rejected under 35 U.S.C. § 101. Compare *In re Musgrave*, 431 F.2d 882, 893, 167 USPQ 280, 289 (CCPA 1970); *In re Foster*, 438 F.2d 1011,1013, 169 USPQ 99, 101 (CCPA 1971). Further, when such a rejection is made, the Office must expressly state how the language of the claims has been interpreted to support the rejection (MPEP 2106(II)(A)).

The Examiner has made no such showing. Applicant respectfully asserts that the written description in the instant application teaches that the claimed databases containing information from only healthy individuals produced by the claimed methods have numerous uses. For example, the specification (page 4, lines 23-26) discloses

> The databases obtained from healthy individuals have numerous uses, such as correlating known polymorphisms with a phenotype or disease. The databases can be used to identify alleles that are deleterious, that are beneficial, and that are correlated with diseases.

Further, the specification (page 5, lines 1-21) discloses

> Also provided herein, is a new use for existing databases of subjects and genotypic and other parameters, such as age, ethnicity, race, and gender. Any database can be sorted according to the methods herein and alleles that exhibit statistically significant correlations with any of the sorting parameters can be identified. It is noted, however, is noted, that the databases provided herein and randomly selected databases will perform better in these methods, since disease-based databases suffer numerous limitations, including their relatively small size, the homogeneity of the selected disease population, and the masking effect of the polymorphism associated with the markers for which the database was selected. Hence, the healthy database provided herein, provides advantages not heretofore recognized or exploited. However, the methods provided herein can be used with a selected database, including disease-based databases, with or without sorting for the discovery and correlation of polymorphisms. In addition, the databases provided herein represent a greater genetic diversity than the

> unselected databases typically utilized for the discovery of polymorphisms and thus allow for the enhanced discovery and correlation of polymorphisms.
>
> The databases provided herein can be used for taking an identified polymorphism, and ascertaining whether it changes in frequency when the data is sorted according to a selected parameter.

The specification further discloses (page 6, lines 9-20)

> The databases and methods provided herein permit, among other things, identification of components, particularly key components, of a disease process by understanding its genetic underpinnings and also permit an understanding of processes, such as individual drug responses. The databases and methods provided herein also can be used in methods involving elucidation of pathological pathways, in developing new diagnostic assays, identifying new potential drug targets, and in identifying new drug candidates.
>
> The methods and databases can be used with experimental procedures, including, but are not limited to, *in silico* SNP identification, *in vitro* SNP identification/verification, genetic profiling of large populations, and in biostatistical analyses and interpretations.

Thus, more than one practical application has been asserted, although only one is necessary to satisfy the utility requirement.

Further, applicant respectfully asserts that the claims encompass at least one of a computer-readable medium, manipulation of *specific* data representing physical objects or activities (pre-computer activity), *specific* independent acts performed, and/or produces a tangible concrete product. Each method claim produces a tangible result—a searchable database– which can be stored on any suitable computer-readable medium. In addition, only claims 4 and 5 are directed to methods. Claims 6-17 are directed to products, and hence, are outside the purview of the rejection.

Claims 4 and 5

Claim 4 is directed to a method for producing a database stored on a computer-readable medium for use in prognosis, diagnosis and for predicting

outcomes based upon a plurality of variables. The method results in a database including sets of variables that are stored on a computer-readable medium, which is a tangible product.

Claim 5 is directed to a method for producing a database which includes obtaining a biological sample, analyzing the sample, and entering the resulting analytical data into the database, which is stored on a computer-readable medium for use in prognosis, diagnosis and for predicting outcomes based upon a plurality of variables. The method results in a database including sets of variables that are stored on a computer-readable medium, which is a tangible product.

Claims 4 and 5 are directed to methods that set forth steps including storing data in a database stored on a computer-readable medium memory. The data includes, for example, the answers to a set of questions, such as the height, weight, age of a healthy subject, and the medical history of the patient, or the results from an analysis of a biological sample obtained from individual healthy subjects. The sets of data are not sets of mathematical variables, but include collections of questions and the corresponding parameters that can be used to sort the database, the results of which are useful, for example, for the discovery and correlation of polymorphisms. Such output is concrete and tangible.

As noted previously, the first steps of the method (pre-computer activity) involves identifying healthy members of a population and collecting data from them, by querying healthy subjects to obtain answers to questionnaires, or performing tests or by making physical observations or chemical measurements to obtain data. This constitutes physical activity. The collected data represents physical objects, not abstract ideas. The data is then associated with each individual subject using a unique indexer, and converted into computer-readable format, and entered into a computer, all of which are activities that constitute manipulation of data representing physical objects or activities (pre-computer

activity). Computer software or systems transform or convert the subject matter representative of or constituting physical activity, into tangible products that result from the processes as an output: healthy-subject databases stored in computer memory. The healthy patient databases resulting from claim 4 or claim 5 constitute tangible products that can be sold for diagnostic purposes.

Therefore, method claims 4 and 5 include steps or products that are indicative of statutory subject matter, such as performance of physical acts, output of tangible products, performance of processes that produce tangible results, and physical manipulations. Each method claim produces a tangible concrete result. Hence, claims 4 and 5 are directed to statutory subject matter.

Claims 6 through 17

Claims 6-8, and claims dependent thereon, are directed to databases. Claim 6 is directed to the database produced by the method of claim 4 and claim 7 is directed to the database produced by the method of claim 5. Claim 8 is directed to a database that includes datapoints representative of a plurality of healthy organisms from whom biological samples are obtained and an indexer that identifies each organism, where each datapoint is associated with data representative of the organism type and other identifying information by the indexer, the database is stored on a computer-readable medium, and the database is sortable.

Claims 6-17 are not method claims. Claims 6-17 are product claims directed to healthy patient databases that are stored on a computer-readable medium, and thus the instantly claimed databases constitute tangible products. The database stored on a computer-readable medium is no less tangible than a heart monitor or immunoassay that is sold for diagnostic purposes. Thus, the products claimed in claims 6-17 encompass tangible products, and are directed to statutory subject matter.

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AMENDMENT

THE REJECTION OF CLAIMS 4-17, 30, 31, AND 43-54 UNDER 35 U.S.C. §102(b)

Claims 4-17, 30, 31, and 43-54 are rejected under 35 U.S.C. § 102(b) as anticipated by Campbell *et al.* (WO 98/35609) because Campbell *et al.* allegedly discloses a computer-based system for predicting the future health of an individual based upon acquiring and analyzing a number of biological and physiological markers. The Examiner contends that the recitation "specified biological condition" in the disclosure of Campbell *et al.* "includes all ranges of health, from robustly healthy to the most severely diseased" and thus discloses a database of data obtained from healthy members of the population. Campbell *et al.* allegedly discloses that the data could include body tissues or fluids or any "biomarker" information, including physiological and biochemical parameters.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 4 is directed to a method of producing a healthy-subject database stored in a computer memory that includes identifying healthy members of a population, obtaining data comprising identifying information and obtaining historical information and data relating to the identified members of the population and their immediate family, entering the data for each member of the population into a database in the memory of a computer, and associating the respective data with the individual member using an indexer. Claim 5, which depends from claim 4, is directed to the method of claim 4 which further includes obtaining a biological sample, analyzing the sample, and entering the analytical results into the database in the memory of a computer.

Claims 6-8 are directed to the healthy subject databases. Claims 6 and 7 are directed to the databases produced by the methods of claims 4 and 5, respectively. Claim 8 is directed to a database that includes datapoints representative of a plurality of healthy organisms from whom biological samples are obtained and an indexer that identifies each organism, where each datapoint is associated with data representative of the organism type and other identifying information by the indexer, the database is stored on a computer-readable medium, and the database is sortable. Claims 9-17 depend from claim 8 and are directed to various embodiments.

Claim 31 is directed to a computer system that includes the database of claim 8.

Claim 32 is directed to a system for high throughput processing of biological samples, which includes a process line with a plurality of processing stations; a robotic system that transports the reaction vessel from processing station to processing station; a data analysis system that receives test results of the process line and automatically processes the test results to make a determination regarding the biological sample in the reaction vessel; a control system that determines when the test at each processing station is complete

and, in response, moves the reaction vessel to the next test station, and continuously processes reaction vessels one after another until the control system receives a stop instruction; and a database of claim 8, wherein the samples tested by the automated process line comprise samples from subjects in the database.

Claim 43 is directed to a method of producing a database stored in a computer memory, which includes identifying healthy members of a population, obtaining identifying and historical information and data relating to the identified members of the population, entering the member-related data into the computer memory database for each identified member of the population and associating the member and the data with an indexer, where the database is a relational database.

Claim 53 is directed to a computer system that includes the database of claim 50, and independent claim 54 is directed to an automated process line that includes the database of claim 50.

Claim 98 is directed to a combination including the database of claim 8 and a mass spectrometer.

Claim 100 is directed to a system for high throughput processing of biological samples, including a database of claim 8, where the samples tested by the automated process line comprise samples from subjects in the database; and a mass spectrometer for analysis of biopolymers in the samples.

Claim 101 is directed to a method for high throughput processing of biological samples, which includes transporting a reaction vessel along a system of claim 32, which includes the database of claim 8.

Disclosure of Campbell *et al.*

Campbell *et al.* discloses a system for predicting the future health of an individual that includes (1) a computer containing a database based on biological and physiological biomarkers of a test population D (identified as having

acquired a specific condition within a specified time or age interval) and sub-population $\bar{D}$ (identified as not having acquired the condition within the specified parameter), and (2) a computer program that manipulates the data in the database. More particularly, the system and method predicts the future health of an individual in a risk group by comparing an individual's profile of biomarkers (such as serum cholesterol) with biomarker values obtained from members of a large test population. Campbell *et al.* discloses a computer-based method for assessing future health risks for a specific individual and for monitoring the preventative measures taken so as to reduce future health risks for that specific individual (page 6, lines 26-29). Campbell discloses a computer program that includes steps for applying a statistical procedure to the biomarkers to classify an individual as having a high probability of acquiring a specified biological condition (page 8, lines 2-7).

Campbell does not disclose a database that includes data from subjects selected on the basis of being healthy. The reference discloses that its database includes "unhealthy" individuals: subpopulation D of the test population identified as having acquired a specified biological condition within a specified period or age interval (page 7, lines 7-11). Campbell does not disclose a combination including a healthy-subject database and a mass spectrometer, or a healthy-subject database and an automated process line. Campbell does not disclose a system for high throughput processing of biological samples including a healthy-subject database. Campbell does not disclose a method of operating a computing device as instantly claimed that produces an output including correlations between a marker of interest and a selected parameter.

Differences between the claimed subject matter and the disclosure of the Campbell *et al.*

Independent claim 4 and its dependent claims are directed to a method of producing a database, which includes information and data from members of a population selected on the basis of being healthy. In contrast, the database of

biomarkers disclosed by Campbell *et al.* is not discriminating, but "is meant to include all ranges of health, from the most robustly healthy to the most severely diseased" (page 22, lines 14-15). The instantly claimed database is directed to populations selected upon apparent health and no detectable infections (page 4, lines 9-12). Campbell *et al.* does not disclose excluding the most severely diseased from its database, nor does the reference provide any motivation for doing so. The database disclosed by Campbell *et al.* includes at least some unhealthy patients. For example, Campbell *et al.* discloses that a subpopulation D of the test population is identified as having acquired (or is going to acquire) a specific biological condition within a specified time period or age interval (diseased group) and a subpopulation $\bar{D}$ is identified as not having acquired (and who will not acquire) the specified biological condition within the specified time period or age interval (page 26, lines 14-21, and page 51, lines 8-13). Statistical analysis comparing different biomarkers to the two groups are performed to determine the likelihood of disease development (page 58, lines 12 through page 60, line 18).

In addition, Campbell *et al.* discloses (page 23, lines 19-23 and line 30 through page 24, line 2):

> One of the further features of the present invention comprises the step of waiting until a substantial number of deaths have occurred in the test population and then selecting those individuals as the ones for whom the biomarker values are to be determined initially. In addition, a group of still living test members may then be selected from the remainder of the test population....This is another of the many special features of the present invention that distinguishes it from any known prior art system. This technique of postponing sample analysis permits postponement of cost until the results obtained tend to have a greater practical value.

Healthy subjects are not dead, nor is it likely that a "substantial number" of healthy subjects would die. Further, the reference discloses

> The database of biomarker values preferably includes information from each individual recording the dates and ages at the times the biomarkers and biomarker samples are collected and recorded,

> accurate information from surveillance of the individual recording each incident of disease, medical condition, medical pathology, or death, including diagnosis and date of incident. The database includes values of biomarkers assessed before, during, and after each incident, where feasible. (Page 21, lines 11-16, emphasis added).

Hence, Campbell *et al.* does not disclose a database containing data obtained from members of a population selected on the basis of them being healthy, and thus, Campbell *et al.* does not disclose every element of the instant claims. Therefore, because Campbell *et al.* does not disclose all elements of the claimed subject matter, Campbell *et al.* does not anticipate any of the pending claims.

REJECTION OF CLAIMS 98 and 99 UNDER 35 U.S.C. §103(a)

Claims 98-99 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Campbell *et al.* in view of Köster *et al.* (U.S. 6,043,031) because Campbell *et al.* allegedly teaches or suggests the use of computer-based system for predicting the future health of an individual based upon acquiring and analyzing a number of biological and physiological biomarkers, and the Examiner contends that although this reference does not teach the use of the database with a mass spectrometer or an automated process line, Köster *et al.* cures this defect. The Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the method of Campbell *et al.* to include the use of a mass spectrometer and an automated process line as taught in Köster *et al.* because the Examiner alleges that Köster *et al.* suggests the use of mass spectrometry to diagnose a predisposition to a disease or to determine identity or heredity. The Examiner further contends that Köster *et al.* teaches the use of simultaneous detections (multiplexing) and parallel processing in order to expedite analysis and that this meets "the limitations of an automated line."

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The Claims

Claim 98 is directed to a combination, including the database of claim 8 and a mass spectrometer.

Claim 99 is directed to the combination of claim 98 that is an automated process line for analyzing biological samples.

Claim 100 is directed to a system for high throughput processing of biological samples that includes an automated process line including a plurality of processing stations, each of which performs a procedure on a biological

sample contained in a reaction vessel; a database of claim 8, wherein the samples tested by the automated process line include samples from subjects in the database; and a mass spectrometer for analysis of biopolymers in the samples.

Differences Between the Claims and the Teachings of the Cited References

Campbell *et al.*

See related section above (page 22).

Köster *et al.*

Köster teaches mass spectrometry processes for detecting a particular nucleic acid in a biological sample, such as identifying a target nucleic acid as being normal or mutant. The reference teaches that in one embodiment, the amplified target detection sites are arranged in a formnat that allows multiple simultaneous detections (multiplexing) as well as parallel processing using oligonucleotide arrays ("DNA chips") (col. 4, lines 20-25).

Köster does not teach or suggest a computer-based database that includes data from subjects selected on the basis of them being healthy.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Campbell *et al.* with the teachings of Köster *et al.* does not result in the instantly claimed systems.

Campbell *et al.* does not teach or suggest a database containing data obtained from members of a population selected on the basis of them being healthy, and Köster *et al.* does not cure this defect. Köster *et al.* does not teach or suggest a database of any kind, and does not teach a computer-based database. In fact, the only mention of a computer in the entire specification is in the Background section, which teaches that a mass spectrometer can transfer data on-line to a computer (col. 2, line 36).

Köster *et al.* teaches that a biological sample refers to any material obtained from any living source (col. 12, lines 1-3), suggesting that diseased subjects are not excluded. Thus, Köster *et al.* does not teach or suggest the selection of subjects on the basis of them being healthy.

Thus, the combination of the teachings of Campbell *et al.* with the teachings of Köster *et al.* does not result in the subject matter of claims 98-100.

Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Braun *et al.*

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Art Unit: 1631

Examiner: Clow, Lori A.

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Michael Lough

ATTACHMENT TO THE AMENDMENT SHOWING MARKED UP PARAGRAPHS AND CLAIMS (37 CFR §1.121)

IN THE SPECIFICATION:

Please amend the paragraph on page 108, lines 15-21, as follows (insertions are underlined, deletions are [bracketed]:

Referring to FIG. 51, a residual error is calculated by taking a root mean square calculation between the Gaussian 293 and the putative peak 290 in the data signal. The calculation is performed on data within one width on either side of a center line of the Gaussian. The residual error is calculated as:

$[\sqrt{(G-R)^2/N}\,]$ $\sqrt{(G-R)^2/N}$

where G is the Gaussian signal value, R is the putative peak value, and N is the number of points from –W to +W. The calculated residual error is used to generate an adjusted signal-to-noise ratio, as described below.

Please amend claims 4, 8, 9, 53, 54 and 100 as follows (insertions are underlined, deletions are [bracketed]:

4. (Amended) A method of producing a database, comprising:

identifying healthy members of a population;

obtaining data comprising identifying information and obtaining historical information and data relating to the identified members of the population and their immediate family;

entering the data for each member of the population into a database [for each member of the population];

[and] associating the member and the data with an indexer; and

storing the database on a computer-readable medium.

5. (Amended) The method of claim 4, further comprising:

obtaining a body tissue, [or] body fluid sample, or other biological sample;

analyzing the body tissue, [or] body fluid, or biological [in the] sample; and

entering the results of the analysis for each member into the database and associating each result with the indexer representative of each member.

8. (Amended) A database, comprising:

datapoints representative of a plurality of healthy organisms from whom biological samples are obtained; and

an indexer that identifies each organism, wherein

a) each datapoint is associated with data representative of the organism type and other identifying information by the indexer;

b) the database is stored on a computer-readable medium; and

c) the database is sortable.

9. (Amended) The database of claim 8, wherein the datapoints comprise [are] answers to questions regarding one or more [of a] parameters selected from the group consisting of ethnicity, age, gender, height, weight, alcohol intake, number of pregnancies, number of live births, vegetarianism [vegetarians], type of physical activity, state of residence and/or length of residence in a particular state, educational level, age of parent at death, cause of parent death, former or current smoker, length of time as a smoker, frequency of smoking, occurrence of a disease in immediate family (parent, siblings, children), use of prescription drugs and/or reason therefor, length and/or number of hospital stays, and exposure to environmental factors.

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AMENDMENT

43. (Amended) A method of producing a database stored in a computer memory, comprising:

identifying healthy members of a population;

obtaining identifying and historical information and data relating to the identified members of the population;

entering the member-related data into the computer memory database for each identified member of the population and associating the member and the data with an indexer, wherein the database is a relational database.

53. (Amended) A computer system, comprising the database of claim 50 [51].

54. (Amended) An automated process line, comprising the database of claim 50 [51].

100. (Amended) A system for high throughput processing of biological samples, comprising:

an automated process line comprising a plurality of processing stations, each of which performs a procedure on a biological sample contained in a reaction vessel;

a database of claim 8, wherein the samples tested by the automated process line comprise samples from subjects in the database; and

a mass spectrometer [spectrometry] for analysis of biopolymers in the samples.